Remarks

The Amendments to the Claims

Claim 1 has been amended to recite mucosal administration of the recited admixture, which incorporates the recitation of originally filed claim 2.

Claims 1, 16, 17, 23, and 33 are amended to recite a protein immunogen. The specification discloses protein immunogens on page 6, lines 15-19.

Claims 15 and 16 have been amended to recite "two different lectins" and "two different protein immunogens," respectively. See page 5, lines 23-24: "If desired, at least 2, 3, 4, or more different immunogens and/or lectins in varying proportions can be included in an admixture." The dependencies of claims 18, 19, 24 and 28 have been corrected.

New claims 32-43 recite members of the Markush groups recited in originally filed claims 4, 5, 10, 11, and 14.

The amendments add no new matter.

The Objection to Claims 18, 19 and 24

Claims 18, 19, and 24 are objected to for failing to further limit the subject matter of a previous claim. The dependencies of claims 18, 19, and 24, as well as that of claim 28, have been corrected. Applicants respectfully request withdrawal of the objection.

The Rejection of Claims 1, 5-12, 16, 21, 22, 24, and 26-28 Under 35 U.S.C. § 102(b)

Claims 1, 5-12, 16, 21, 22, 24, and 26-28 stand rejected under 35 U.S.C. § 102(b) as anticipated by Shionoya *et al.*, U.S. Patent 4,414,201 ("Shionoya"). Claim 26 has been canceled. Applicants respectfully traverse the rejection of claims 1, 5-12, 16, 21, 22, 24, 27, and 28.

A claim is anticipated only if each and every element as set forth in the claim is expressly or inherently described in a single prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F. 2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed Cir. 1987). Independent claim 1 as amended recites a method of producing an immune response in a mammal comprising administering mucosally to a mammal an admixture comprising a protein immunogen and a plant lectin.

Shionoya teaches administration of a mixture comprising an antigen and the plant lectin abrin. Col. 1, lines 50-59. But Shionoya does not teach mucosal administration of the mixture. Shionoya contains the following teaching regarding routes of administration:

> Abrin in accordance with this invention may be administered together with various antigens, and the preferred route of administration is subcutaneous, intramuscular or intraperitoneal. Furthermore, abrin can be administered separately from an antigen, and in this case, intravenous and intrapleural administrations are possible in addition to the aforesaid administration routes. Or it may be administered directly to a tumor region.

Col. 2 lines 15-16. None of these routes of administration is a mucosal route.

Shionoya does not disclose each element of amended claim 1. Thus, Shionoya does not anticipate claim 1 or dependent claims 5-12, 16, 21, 22, 24, 27, and 28.

Applicants respectfully request withdrawal of the rejections.

The Rejections Under 35 U.S.C. § 103(a)

The Office Action makes four rejections under 35 U.S.C. § 103(a):

- claims 2, 3, 13, 14, 17-19, 23, and 25 stand rejected over Shionoya in view of O'Hagan *et al.*, *Vaccine 17*, 2229-36, 1999 ("O'Hagan");
- claim 4 stands rejected over Shionoya in view of Carrano *et al.*, U.S. Patent 5,962,428 ("Carrano");
- claim 15 stands rejected over Shionoya in view of Gough and Platt, U.S. Patent 4,470,967 ("Gough"); and
- claim 29 stands rejected over Shionoya in view of O'Hagan *et al.*, U.S. Patent 5,603,960 .

To advance prosecution, claims 2 and 29 have been canceled. Applicants respectfully traverse each of the other three rejections.

The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. The *prima facie* case requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142. In none of the rejections has the U.S. Patent and Trademark Office established a *prima facie* case.

The Rejection of Claims 2, 3, 13, 14, 17-19, 23, and 25

Dependent claims 2, 3, 13, 14, 17-19, 23, and 25 stand rejected as obvious over Shionoya in view of O'Hagan. Claim 2 has been canceled. The U.S. Patent and Trademark Office has not established that claims 3, 13, 14, 17-19, 23, and 25 are *prima facie* obvious. First, the asserted motivation for combining the teachings of Shionoya and O'Hagan is legally insufficient.

Second, even if one of ordinary skill in the art would have combined these teachings, she would not have had a reasonable expectation that mucosal administration of an admixture comprising a protein immunogen and a plant lectin would result in an immune response to the protein immunogen which is "greater relative to the immune response to the protein immunogen produced in the absence of the plant lectin," as recited in the rejected claims.

Each of the rejected claims is ultimately dependent on claim 1. Claim 1 is directed to a method of producing an immune response in a mammal. An admixture comprising a protein immunogen and a plant lectin is administered mucosally to a mammal. The mammal thereby produces an immune response to the protein immunogen which is greater relative to the immune response to the protein immunogen produced in the absence of the plant lectin.

The Office Action cites Shionoya as teaching a method for the production of immune responses in mammals by administering an admixture comprising an immunogen and the plant lectin abrin. The Office Action cites O'Hagan as disclosing intranasal immunization protocols using a viral immunogen and a known adjuvant, as well as detection of antibody titers by ELISA. Office Action, paragraph bridging pages 3 and 4. The Office Action asserts that it would have been *prima facie* obvious to one having ordinary skill in the art to substitute the abrin adjuvant of Shionoya for the MF59 adjuvant in the immunization protocol of O'Hagan. Office Action, paragraph bridging pages 3 and 4.[1] The asserted motivation for combining the teachings of

[1] Applicants believe the Office Action meant to refer to the LKT63 adjuvant, because the MF59 adjuvant was used only in intramuscular (non-mucosal) administrations. O'Hagan evaluated the ability of a known mucosal adjuvant (the *E. coli* heat-labile enterotoxins LTK63) to induce protection in a guinea pig model against *Herpes simplex* virus type 2 (HSV2). Page 2229, col. 2, last 5 lines. Protection obtained after intranasal administration of recombinant HSV2 gD2 protein and LTK63 was compared to that obtained after intramuscular administration of gD2 and the adjuvant MF59. Page 2230, col. 1, lines 2-6.

Shionoya and O'Hagan is that abrin induces strong humoral and cellular immune responses to various immunogens. *Id.*

The asserted motivation is legally insufficient. While Shionoya teaches that abrin has an immunopotentiating effect, the only administration routes taught for an admixture of abrin and an antigen are subcutaneous, intramuscular, and intraperitoneal. Col. 2, lines 9-12. None of these routes is a mucosal route. The additional routes taught for separate administration of abrin and an antigen (intravenous and intrapleural; col. 2, lines 12-16) are not mucosal routes. The only other route of administration taught in Shionoya is intratumoral (col. 2, lines 16-17), which also is not a mucosal route. There is nothing in Shionoya that would suggest to the ordinary artisan that an admixture of abrin and an antigen would be effective if administered mucosally. O'Hagan contains no teaching at all regarding plant lectin adjuvants; the only adjuvants taught in O'Hagan are labile enterotoxins. Thus, one of ordinary skill in the art who read both Shionoya and O'Hagan would not have been motivated to combine their teachings.

Even if these references were *arguendo* combined, the ordinary artisan would not have reasonably expected that mucosal administration of an admixture of abrin and the gD2 antigen would result in an immune response to the gD2 which is greater relative to the immune response in the absence of abrin. One of ordinary skill in the art would have been aware of all previous work in the field of plant lectins, immune responses, and adjuvants. *Ex parte Hiyamizu*, 10 U.S.P.Q. 2d 1393, 1394 (Bd. Pat. App. & Inter. 1988). This previous work included that reported in Giannasca *et al.*, *Infection and Immunity*, Oct. 1997, pp. 4288-98 ("Giannasca," of record). Giannasca teaches that, while conjugated lectin-immunogens administered mucosally greatly enhance immune responses, lectin-immunogen admixtures do not show an immune response significantly different from that of a control (p. 4296, Fig. 7). In view of these results,

the ordinary artisan would not reasonably have expected that an admixture of a plant lectin and a protein immunogen would have resulted in an immune response to the protein immunogen that is greater relative to the immune response in the absence of the plant lectin, as recited in the rejected claims.

The Office Action has not provided a legally sufficient motivation for the ordinary artisan to have combined the teachings of Shionoya and O'Hagan, nor would there have been a reasonable expectation that such a combination would have been successful. Thus, the subject matter of claims 3, 13, 14, 17-19, 23, and 25 is not obvious over the combination of Shionoya and O'Hagan.

Applicants respectfully request withdrawal of the rejection over Shionoya in view of O'Hagan.

The Rejection of Claim 4

Dependent claim 4 stands rejected as obvious over Shionoya in view of Carrano. A *prima facie* case that claim 4 is obvious over the combination of Shionoya and Carrano has not been made. First, the asserted motivation for combining the teachings of Shionoya and Carrano is legally insufficient. Second, even if one of ordinary skill in the art would have combined these teachings, she would not have had a reasonable expectation that mucosal administration of an admixture comprising an immunogen and a plant lectin would result in an immune response to the immunogen which is "greater relative to the immune response to the immunogen produced in the absence of the plant lectin."

Claim 4 depends from claim 1. Claim 1 as amended recites a "protein immunogen." Dependent claim 4 as amended recites a ML-I; new claims 32-35 recite ML-II, ML-III, WGA, and UEA-1, respectively, from which the plant lectin recited in independent claim 1 can be

chosen. The combination of Shionoya and The Office Action cites Shionoya as teaching a method for the production of immune responses in mammals by administering an admixture comprising an immunogen and a plant lectin. The Office Action concedes that Shionoya does not teach the use of a lectin from the recited group. Page 4, lines 20-22. The Office Action cites Carrano as disclosing immunogenic compositions comprising a lectin. The Office Action asserts that it would have been *prima facie* obvious to one having ordinary skill in the art to prepare an immunogenic composition comprising the immunogen of Shionoya and one of the adjuvants provided by Carrano.

The ordinary artisan would not have been motivated to combine the teachings of Shionoya and Carrano. Shionoya teaches use of a protein antigen (BSA; Examples 1-4) and whole cells (irradiated tumor cells; Example 5). In contrast, Carrano teaches methods of introducing ***nucleic acid molecules*** into animal cells for use as genetic vaccines. Column 3, lines 9-16. The Office Action has not provided a motivation sufficient for the ordinary artisan to have combined such different teachings. The Office Action also has not established that the ordinary artisan would have reasonably expected that a lectin useful for immunizations with ***genetic material*** also would be useful to potentiate an immune response against a ***protein antigen***.

Applicants respectfully request withdrawal of the rejection over Shionoya in view of Carrano.

The Rejection of Claim 15

Dependent claim 15 stands rejected as obvious over Shionoya in view of Gough. To establish *prima facie* case that claim 15 is obvious, all the claim limitations must be taught or

suggested by the prior art. *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 584 (CCPA 1974). The combination of Shionoya and Gough does not teach or suggest all the elements of claim 15.

Claim 15 is dependent on claim 1. As amended, claim 1 recites mucosal administration. Claim 15 recites an admixture comprising two or more lectins. The Office Action cites Shionoya as teaching a method for the production of immune responses in mammals by administering an admixture comprising an immunogen and a plant lectin. The Office Action cites Gough as teaching immunogenic compositions comprising a lectin, which are useful for stimulating T and B cell mitogenesis. Page 5, first paragraph.

The Office Action concedes that Shionoya discloses neither intranasal (*i.e.*, mucosal) administration (page 3, last paragraph), nor immunogenic compositions comprising two or more lectins (page 5, lines 4-5). Gough teaches glycoprotein-lectin complexes. *See, e.g.*, col. 2, lines 11-14, and col. 3, line 46, to col. 4, line 53. Gough does not teach or suggest mucosal administration. Gough teaches that "[t]he dose form of the vaccine should be an injectable liquid suspension. The mode of injection may be subcutaneous or intramuscular, or other parenteral injection site." Col. 5, lines 4-7. Gough also does not teach or suggest the use of two different lectins.

The cited combination does not teach or suggest all elements recited in claim 15. Thus, claim 15 is not obvious over the combination of Shionoya and Gough.

Applicants respectfully request withdrawal of the rejection over Shionoya in view of Gough.

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